Public Assessment Report

Decentralised Procedure

SALINE NEBULISER SOLUTION
(SODIUM CHLORIDE 0.9% W/V)

UK/H/2088/001/DC
UK licence no: PL 18023/0006

BREATHE LIMITED
LAY SUMMARY

On 23rd October 2009, the MHRA granted Breath Limited a Marketing Authorisation (licence) for the medicinal product Saline Nebuliser Solution (Sodium Chloride 0.9% w/v). This prescription-only product (POM) is used to dilute medicines that are used in a nebuliser.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Saline Nebuliser Solution (Sodium Chloride 0.9% w/v) outweigh the risks; hence a Marketing Authorisation has been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Quality aspects</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Non-clinical aspects</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>Clinical aspects</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Overall conclusions</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>Steps taken after initial procedure</td>
<td></td>
</tr>
</tbody>
</table>
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Saline Nebuliser Solution (Sodium Chloride 0.9% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10a, Well-established use</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Sodium chloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Nebuliser solution</td>
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<tr>
<td><strong>Strength</strong></td>
<td>0.9% sodium chloride</td>
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<td><strong>MA Holder</strong></td>
<td>Breath Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ</td>
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<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
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<td><strong>Concerned Member States</strong></td>
<td>Malta</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/2088/001/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 150 – 15th August 2009</td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Saline Nebuliser Solution
(Sodium Chloride 0.9% w/v)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml of solution contains 9 mg of Sodium Chloride
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Solution for nebulisation
Clear, colourless solution in a clear, plastic single dose ampoule

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For dilution of solutions for nebulisation.

4.2 Posology and method of administration
Adults, children and elderly: use as directed by the physician.

Saline Nebuliser Solution is only to be used as a diluent for diluting products for nebulisation and should not be used on its own. It should not be taken orally or administered parenterally.

Each ampoule contains 2.5 ml of solution.

Refer to the patient information leaflet of the nebulised product to be diluted that your physician has prescribed you for detailed instructions on use of this solution as a diluent. To ensure accurate dosing it is recommended that a dosing syringe is used if necessary.

Method of Administration: By inhalation from a suitable nebuliser or an intermittent positive pressure ventilator after the single dose ampoule has been opened and its contents transferred to the nebuliser chamber. Administration should be in accordance with the manufacturer’s instructions for the device.

1. Prepare the nebuliser by following the manufacturer's instructions and the advice of your doctor.
2. The nebulised product to be diluted should be introduced into the nebuliser chamber as instructed in the appropriate patient information leaflet.
3. Carefully separate a new saline ampoule from the strip. Never use an ampoule that has been opened already.
4. Open the ampoule by simply twisting off the top, always taking care to hold it in an upright position.
5. Squeeze the contents of the plastic ampoule or use a dosing syringe as required into the nebuliser chamber and swirl gently to mix.
6. Assemble the nebuliser and use it as directed by your doctor.

As the single dose units contain no preservatives it is important that the contents are used immediately after opening and a fresh ampoule is used for each administration to avoid microbial contamination. Partly used, opened or damaged single dose units should be discarded.

Any solution remaining in the nebuliser chamber should be discarded.

4.3 Contraindications
The solution should not be administered orally or parenterally.
4.4 Special warnings and precautions for use
Do not use unless the product is clear and the pack intact. Discard any surplus after use. Saline Nebuliser Solution should be used with a nebuliser, only under the direction of a physician. Patients using nebuliser solutions at home should be warned that if the usual relief is diminished or the usual duration of action reduced, they should consult their doctor.

4.5 Interaction with other medicinal products and other forms of interaction
Not known.

4.6 Pregnancy and lactation
As with most medicines, consult your doctor first if you are pregnant or breastfeeding.

4.7 Effects on ability to drive and use machines
Not known.

4.8 Undesirable effects
Saline Nebuliser Solution is not expected to cause any undesirable effects in normal use.

4.9 Overdose
Substantial oral ingestion may require the use of a diuretic to remove excess sodium.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Isotonic (0.9% w/v) sodium chloride solution is widely used for dilution purposes.

5.2 Pharmacokinetic properties
Not applicable

5.3 Preclinical safety data
There are no findings of relevance to the prescriber other than those already mentioned elsewhere in the SPC. Please refer to the product to be reconstituted.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Water for Injections

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

Ampoules removed from the foil overwrap should be used within 90 days.

Use immediately after first opening of the ampoule. Discard any unused contents.

6.4 Special precautions for storage
Do not store above 25°C.
Do not refrigerate or freeze.

6.5 Nature and contents of container
A unit dose blow moulded hermetically sealed low density polyethylene ampoule containing 2.5 ml of solution. Strips of ten ampoules are overwrapped in an aluminium laminate foil pack. Saline Nebuliser Solution is available in boxes containing 20, 60 or 100 ampoules.

6.6 Special precautions for disposal
No special requirements.
7 MARKETING AUTHORISATION HOLDER
Breath Limited
Unit 2, Eastman Way,
Stevenage,
Hertfordshire,
SG1 4SZ
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 18023/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/10/2009

10 DATE OF REVISION OF THE TEXT
23/10/2009
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Saline Nebuliser Solution
Sodium chloride 0.9% w/v

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT SALINE NEBULISER SOLUTION IS AND WHAT IT IS USED FOR

Saline Nebuliser Solution is a solution of sodium chloride, that is, salt water. It is used to dilute medicines that are used in your nebuliser.

Remember, you should also read the leaflet for these medicines before diluting them with Saline Nebuliser Solution.

2. BEFORE YOU USE SALINE NEBULISER SOLUTION

Saline Nebuliser Solution should only be used in your nebuliser and following the directions of your doctor.

Do not swallow Saline Nebuliser Solution. The solution should never be given by injection.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, talk to your doctor before using this medicine.

Important information about some of the ingredients of Saline Nebuliser Solution

This medicinal product is a solution of salt and this needs to be taken into consideration by patients on a controlled sodium (salt) diet.

3. HOW TO USE SALINE NEBULISER SOLUTION

Always use Saline Nebuliser Solution exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

You must only use Saline Nebuliser Solution in a nebuliser. The nebuliser turns the solution into a fine mist which you can breathe in. Always read the manufacturer’s instructions and make sure you know how to use the nebuliser before you take your medicine.

1. Prepare your nebuliser for use according to the instructions provided by the manufacturer and the advice given by your doctor.
2. The nebulised product that you will dilute should be placed into the nebuliser chamber as instructed in the patient information leaflet of that product.
3. Carefully remove an ampoule of Saline Nebuliser Solution from the labelled strip by twisting and pulling (diagram 1). Never use an ampoule that has already been opened.

4. Open the ampoule by twisting off the top, taking care to hold it in an upright position (diagram 2).
5. Squeeze the contents of the ampoule (or dosing syringe if you are using one) into the nebuliser chamber and swirl the contents of the nebuliser gently to mix.
6. Use your nebuliser according to the manufacturer’s instructions and as advised by your doctor.
7. After you have used your nebuliser, throw away any solution that is left in the reservoir.
8. Clean your nebuliser thoroughly according to the manufacturer’s instructions.

As there are no preservatives in Saline Nebuliser Solution, it is important that you use the contents of the ampoule immediately after opening and that you mix up a fresh batch of the solution before each dose. Discard any partly used, opened or damaged ampoules and any solution remaining in the nebuliser chamber after use.

Do not swallow the solution or use it in injections.

Follow your doctor’s instructions when you are diluting medicines for use in your nebuliser and refer to the patient information leaflet of the product to be diluted for more detailed instructions on using saline solution for dilution.

If you are using your nebuliser at home, and you find that you are not getting your usual amount of relief or the relief does not last as long, consult with your doctor.

If you use more Saline Nebuliser Solution than you think you should or accidentally swallow it: Contact your doctor or hospital immediately. Take any remaining solution or this leaflet with you so the medical staff know exactly what you have taken.

4. POSSIBLE SIDE EFFECTS

It is unlikely that Saline Nebuliser Solution will cause any side effects. However, if you think you may have developed a side effect please tell your doctor or pharmacist.

The medicine you breathe in with Saline Nebuliser Solution could cause some side effects. The leaflet that comes with that medicine will give you more information on this.
5. HOW TO STORE SALINE NEBULISER SOLUTION

Keep out of the reach and sight of children.

Do not store above 25°C. Do not refrigerate or freeze.

Do not use this medicine if the solution is cloudy or after the expiry date as stated on the carton.

The expiry date refers to the last day of that month.

Ampoules removed from the foil overwrap should be used within 90 days.

Use the solution immediately after first opening the ampoule.

Medicines should not be disposed of via wastewater or household waste.

Ask your pharmacist how to dispose of medicines no longer required.

These measures will help to protect the environment.

4. FURTHER INFORMATION

What Saline Nebuliser Solution contains
- The active substance is sodium chloride 0.9% w/v. Each 1 ml of solution contains 9 mg of sodium chloride.
- The other ingredient is Water for Injections.

What Saline Nebuliser Solution looks like and contents of the pack
Saline Nebuliser Solution is supplied as a unit dose blow moulded hermetically sealed plastic ampoule containing 2.1 ml of solution.
Strips of ten ampoules are overwrapped in an aluminium laminate foil pack.
Saline Nebuliser Solution is available in boxes containing 20, 60 or 100 ampoules.

Marketing Authorisation Holder: Breathe Limited
Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, UK.

Manufacturer: Laboratoires Unither
Zone Industrielle, 10 Rue Andre Dumucier, 80852 Amiens, Cedex 2, France.

This leaflet was last approved in 10/2009.
Module 4
Labelling

Saline Nebuliser Solution
(Sodium chloride 0.9% w/v)
20 x 2.5ml ampoules
FOR INHALATION USE ONLY

Each 2.5ml ampoule contains
sodium chloride 0.9% w/v in water for injections.
Solution for nebulisation
FOR INHALATION USE ONLY

PAR Saline Nebuliser Solution (Sodium Chloride 0.9% w/v) UK/H/2088/001/DC

10
Saline Nebuliser Solution
(Sodium chloride 0.9 % w/v)

Each 2.5 ml ampoule contains sodium chloride 0.9% w/v.
Each 1 ml of solution contains 9 mg of sodium chloride.
Other ingredients: water for injections.

For dilution of solutions for nebulisation. Sterile until opened.
IMPORTANT: Read the enclosed leaflet before use.
Do not store above 25°C. Do not refrigerate or freeze.
Use as directed by the doctor. Discard any unused contents after use.

10 x 2.5ml ampoules

FOR INHALATION USE ONLY

Solution for nebulisation
Keep out of the reach and sight of children

Marketing Authorisation Holder:
Breath Limited,
Unit 2, Eastman Way,
Stevenage, Hertfordshire,
SG1 4SZ, U.K.
PL 18023/0006
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK and Malta agreed to grant a marketing authorisation for the medicinal product Saline Nebuliser Solution (Sodium Chloride 0.9% w/v) on 15th August 2009. This product was assessed by the Decentralised Procedure (UK/H/2088/001/DC), with the UK as Reference Member State. A subsequent national licence was granted in the UK on 23rd October 2009.

The product is a prescription-only product for dilution of solutions for nebulisation.

This is an application made under Article 10a of 2001/83 EC, as amended, a well-established use application for a diluent of solutions for nebulisation.

The product contains the active ingredient sodium chloride.

No new preclinical studies were conducted, which is acceptable given that the application is submitted under Article 10a, a well-established use application.

No clinical studies were conducted, which is acceptable given that the application is submitted under Article 10a, a well-established use application.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The decentralised procedure was completed at Day 150 (15th August 2009), with the reference member state and all concerned member states agreeing that the licence was approvable. The national phase of the decentralised procedure was completed in the UK on 23rd October 2009.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Saline Nebuliser Solution (Sodium Chloride 0.9% w/v)</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Sodium chloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Solvents and diluting agents (V07 AB)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>0.9% w/v</td>
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<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/2088/001/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
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<td>Member States concerned</td>
<td>Malta</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 18023/0006</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Breath Limited</td>
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III III.1 SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance
INN: Sodium chloride
Other names: Common salt, table salt, halite
CAS Registry No: 7647-14-5
Molecular Formula: NaCl
Molecular Weight: 58.443
Appearance: White or colourless crystals, freely soluble in water, practically insoluble in ethanol

Sodium chloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance sodium chloride that is in compliance with the European Pharmacopoeia monograph. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications have been provided for all packaging used to store the active substance. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

A suitable retest period has been assigned, based on stability data from studies performed in-line with current guidelines.

P Medicinal Product
Other Ingredients
Other ingredients consist of the pharmaceutical excipient water for injections. This excipient complies with its European Pharmacopoeia monograph. No materials of animal or human origin are used in the production of water for injections.

Pharmaceutical Development
The applicant has provided a suitable product development rationale and data.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and has shown satisfactory results.
Control of Drug Product
The finished product specification proposed is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Satisfactory data on the characterisation of impurities have been provided.

Reference Standards or Materials
Certificates of analysis for all reference standards used have been provided and are satisfactory.

Container Closure System
The finished product is packaged into blow-moulded hermetically sealed low-density polyethylene ampoules containing 2.5ml of solution. Strips of 10 ampoules are overwrapped in aluminium laminate foil packs and packaged in pack sizes of 20, 60 or 100 ampoules.

Stability of the Drug Product
Stability data have been provided to support a shelf-life of 24 months, with the storage instructions “Do not store above 25°C” and “Do not refrigerate or freeze”.

Ampoules removed from the foil overwrap should be used within 90 days and contents of ampoules should be used immediately after opening. Any unused contents should be discarded.

Bioequivalence/Bioavailability
Certificates of analysis have been provided for batches of test and reference product used in the bioequivalence studies.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS
Sodium chloride is widely used as a diluent for medical solutions, including those to be delivered via a nebuliser. The proposed product is not indicated on the basis of a claim of efficacy but purely as a diluent for nebuliser solutions. The safety of sodium chloride is well-established having been in clinical use for many years. As such, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The preclinical expert report has been written by an appropriately qualified person and is a suitable summary of the preclinical aspects of the dossier.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY/EFFICACY
Saline solution has been used for over 30 years as a diluent for nebulised active products.

It is a well-established fact that inhaled hypertonic saline is beneficial in restoring airways surface liquid in cystic fibrosis patients, and thereby increasing mucociliary clearance and improving lung function.

No new studies have been submitted and none are required for an application of this type.

SAFETY
There are no new or unexpected clinical safety concerns with the use of this product. The good safety profile accounts for the widespread use as a diluent. The summary of product characteristics incorporates no safety warnings or potential side effects from the use of this product as a diluent, and this is appropriate. Likewise, there are no cautions with use in pregnancy, driving, etc.

In the UK dietary reference values have been published for sodium. The reference nutrient intake for adults is 1.6g of sodium (70 mmol) daily. The minimal quantities that would enter the circulation from inhaled diluent of 0.9% sodium chloride would not impact this daily intake. The obvious and well-known side effect of an excess of salt intake would be development of high blood pressure, but the content of the diluent would have to be excessive to cause such a concern. Indeed, 0.9% saline has been used twice daily as a control in a 48-week study investigating the long-term effects of inhaled hypertonic saline in patients with cystic fibrosis with no adverse events of concern reported as purely due to normal saline.

EXPERT REPORT
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified physician.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is satisfactory and consistent with the SPC of similar products.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory and consistent with the SPC.

LABELLING
These are satisfactory.

CONCLUSION
The efficacy of this product is not of question as Saline Nebuliser Solution (Sodium Chloride 0.9% w/v) is used as a diluent for other medicinal products used for nebulisation.

The safety of saline as a nebuliser diluent has been well-established for many years now, and there is no new information that would suggest that the profile has changed. Saline solution is used in a widespread manner as the diluent of choice for nebulisers.

The benefit-risk balance is therefore favourable and this product is approvable.

The SPC, PIL and packaging are satisfactory and consistent with those for the reference product.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Saline Nebuliser Solution (Sodium Chloride 0.9% w/v) are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
No new clinical data were submitted and none are required for an application of this type.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for other similar products.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The safety of saline as a nebuliser diluent has been well-established for many years now, and there is no new information that would suggest that the profile has changed. The risk-benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Scope</th>
<th>Outcome</th>
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